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(54) Title: SMAC-PEPTIDES AS THERAPEUTICS AGAINST CANCER AND AUTOIMMUNE DISEASES

(57) **Abstract:** The invention is directed to the use of Smac to sensitize different tumors and self-reactive immune cells to various pro-apoptotic stimuli, in that the cells subsequently undergo apoptosis. Therefore, Smac can be used as a compound for the manufacture of a medicament for the treatment of cancer and autoimmune diseases. Sensitization of the cells is achieved either by applying a cell-permeable form of Smac combined with known anticancer agents or by overexpression of the protein. It is an object of the invention to provide a new method in cancer and autoimmune disease therapy by using Smac agonists for apoptosis regulation. Thus, Smac agonists represent novel promising cancer and autoimmune disease therapeutics to potentiate the efficacy of cytotoxic therapies even in resistant tumors and immune cells.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/04039

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	C12N15/12	C12N15/62	A61K47/48	C07K5/103	C07K19/00
	C07K14/47	A61K38/17	C07K5/10	A61K41/00	

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/16418 A (THOMAS JEFFERSON UNIVERSITY, USA) 28 February 2002 (2002-02-28) examples claims -----	1-11, 13-36
X	WO 02/16402 A (BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM, USA) 28 February 2002 (2002-02-28) examples claims -----	1-36
X	WO 02/26775 A (TRUSTEES OF PRINCETON UNIVERSITY, USA) 4 April 2002 (2002-04-04) examples claims ----- -/-	1-11, 13-36

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

4 March 2004

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/04039

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/49719 A (UNIV TEXAS SYSTEM) 12 July 2001 (2001-07-12) examples -----	1-11, 13-36
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2001, ENDO, HITOSHI ET AL: "Cysteine, basic and neutral amino acid transporter BAT1 from rat and human activated by rBAT, cDNA, and recombinant expression" XP002204777 retrieved from STN Database accession no. 134:174559 HCA abstract -& JP 2001 046070 A (FOUNDATION FOR SCIENTIFIC TECHNOLOGY PROMOTION, JAPAN) 20 February 2001 (2001-02-20) -----	1-11, 13-36
Y	WO 00/58488 A (DALBY BRIAN ;INVITROGEN CORP (US); BENNETT ROBERT P (US)) 5 October 2000 (2000-10-05) examples claims -----	1-11, 13-36
Y	WO 01/38547 A (ROSENECKER JOSEPH ;PLANK CHRISTIAN (DE); RITTER WOLFGANG (DE); RUD) 31 May 2001 (2001-05-31) examples claims -----	1-11, 13-36
Y	WO 00/29427 A (CYCLACEL LTD ;FISCHER M PETER (GB); ZHELEV NIKOLAI (GB)) 25 May 2000 (2000-05-25) examples claims -----	1-11, 13-36
Y	WO 99/05302 A (PERKIN ELMER CORP) 4 February 1999 (1999-02-04) examples claims -----	1-11, 13-36
Y	DEROSSI D ET AL: "TROJAN PEPTIDES: THE PENETRATIN SYSTEM FOR INTRACELLULAR DELIVERY" TRENDS IN CELL BIOLOGY, ELSEVIER SCIENCE LTD, XX, vol. 8, February 1998 (1998-02), pages 84-87, XP002940006 ISSN: 0962-8924 abstract figure 2 page 86, right-hand column, last paragraph - page 87, left-hand column, line 4 -----	1-11, 13-36

-/-

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International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>SCHWARZE S ET AL: "In vivo protein transduction: delivery of a biologically active protein into the mouse" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 285, no. 5433, 3 September 1999 (1999-09-03), pages 1569-1572, XP002140133 ISSN: 0036-8075 abstract page 1571</p> <p>-----</p> <p>FISCHER P M ET AL: "STRUCTURE-ACTIVITY RELATIONSHIP OF TRUNCATED AND SUBSTITUTED ANALOGUES OF THE INTRACELLULAR DELIVERY VECTOR PENETRATIN" JOURNAL OF PEPTIDE RESEARCH, MUNKSGAARD INTERNATIONAL PUBLISHERS, COPENHAGEN, DK, vol. 55, no. 2, February 2000 (2000-02), pages 163-172, XP000899124 ISSN: 1397-002X the whole document</p> <p>-----</p>	1-11, 13-36
X	<p>FULDA SIMONE ET AL: "Release of Smac from mitochondria bypasses the Bcl-2 inhibition in type II cells and sensitizes for death receptor or drug-induced apoptosis." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, vol. 42, March 2001 (2001-03), page 552, XP002251122 ISSN: 0197-016X abstract & 92nd Annual Meeting of the American Association for Cancer Research; New Orleans, LA, USA; March 24-28, 2001 abstract</p> <p>-----</p> <p>FULDA SIMONE ET AL: "Smac release from mitochondria bypasses the Bcl-2 inhibition and sensitizes tumor cells for death receptor or drug-induced apoptosis." BLOOD NOVEMBER 16, 2001, vol. 98, no. 11 Part 1, 16 November 2001 (2001-11-16), pages 572a-573a, XP002251123 ISSN: 0006-4971 abstract & 43RD ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEMATOLOGY, PART 1, 7 December 2001 (2001-12-07), ORLANDO, FLORIDA, USA</p> <p>-----</p>	1-11, 13-36
		-/-

INTERNATIONAL SEARCH REPORT

International Application No.
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FULDA SIMONE ET AL: "Smac peptides or Smac gene transfer as a novel strategy to overcome resistance against TRAIL- or drug-induced apoptosis." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, vol. 43, March 2002 (2002-03), pages 527-528, XP002251124 ISSN: 0197-016X abstract & 93rd Annual Meeting of the American Association for Cancer Research; San Francisco, California, USA; April 06-10, 2002 abstract	1-11, 13-36
A	JOHNSTONE RICKY W ET AL: "Apoptosis: A link between cancer genetics and chemotherapy." CELL, vol. 108, no. 2, 25 January 2002 (2002-01-25), pages 153-164, XP002251125 ISSN: 0092-8674 figure 2	1-11, 13-36
X, P	IGNEY FREDERIK H ET AL: "Death and anti-death: Tumour resistance to apoptosis." NATURE REVIEWS CANCER, vol. 2, no. 4, 20 April 2002 (2002-04-20), pages 277-288, XP002251126 ISSN: 1474-175X figure 4	1-11, 13-36
X, P	FULDA SIMONE ET AL: "Smac agonists sensitize for Apo2L/TRAIL- or anticancer drug-induced apoptosis and induce regression of malignant glioma in vivo." NATURE MEDICINE, vol. 8, no. 8, August 2002 (2002-08), pages 808-815, XP002251127 ISSN: 1078-8956 abstract page 810, right-hand column - page 811, left-hand column page 811, right-hand column, paragraph DISCUSSION - page 814, left-hand column; figure 5	1-11, 13-36
Y	US 6 306 613 B1 (BAIRD ANDREW ET AL) 23 October 2001 (2001-10-23) column 63; example 16	1-11, 13-36
		-/-

INTERNATIONAL SEARCH REPORT

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PCT/EP 03/04039

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 903 408 A (BIOGEN INC) 24 March 1999 (1999-03-24) figures 3,7 -----	1-11, 13-36
Y	WO 94/04686 A (BARSOUM JAMES G ; BIOGEN INC (US); FAWELL STEPHEN E (US); PEPINSKY R B) 3 March 1994 (1994-03-03) examples 2,4,5,7,13,16 claims 3,16,18,21 -----	1-11, 13-36
X	J. SILKE ET AL.: "The anti-apoptotic activity of XIAP is retained upon mutation of both the caspase 3- and caspase 9-interacting sites" JOURNAL OF CELL BIOLOGY, vol. 157, no. 1, 1 April 2002 (2002-04-01), pages 115-124, XP002272040 ISSN: 0021-9525 abstract page 118, right-hand column, last paragraph - page 119, left-hand column page 122, paragraph DISCUSSION - page 123 -----	1-36
X	EKERT P G ET AL.: "DIABLO promotes apoptosis by removing MIHA/XIAP from processed caspase 9" JOURNAL OF CELL BIOLOGY, vol. 153, no. 3, 30 April 2001 (2001-04-30), pages 483-490, XP002272041 ISSN: 0021-9525 abstract page 485, right-hand column - page 486, right-hand column, line 5 page 487, right-hand column, last paragraph - page 488, left-hand column -----	1-36
X	SRINIVASULA S M ET AL: "A conserved XIAP-interaction motif in caspase-9 and Smac/DIABLO regulates caspase activity and apoptosis" NATURE, vol. 410, 1 March 2001 (2001-03-01), pages 112-116, XP002962286 ISSN: 0028-0836 abstract; figures -----	1-36

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/04039

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>VERHAGEN A M ET AL: "HtrA2 promotes cell death through its serine protease activity and its ability to antagonize inhibitor of apoptosis proteins" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 277, no. 1, 4 January 2002 (2002-01-04), pages 445-454, XP002957689 ISSN: 0021-9258 page 445 figures page 453, paragraph DISCUSSION – page 454 -----</p>	1-36
Y	<p>HOLCIK M ET AL: "TRANSLATION UPREGULATION OF X-LINKED INHIBITOR OF APOPTOSIS (XIAP) INCREASES RESISTANCE TO RADIATION INDUCED CELL DEATH" ONCOGENE, vol. 19, no. 36, 24 August 2000 (2000-08-24), pages 4174-4177, XP008007068 ISSN: 0950-9232 the whole document -----</p>	1-36
Y	<p>VERHAGEN ANNE M ET AL: "Identification of DIABLO, a mammalian protein that promotes apoptosis by binding to and antagonizing IAP proteins" CELL, vol. 102, no. 1, 7 July 2000 (2000-07-07), pages 43-53, XP002175397 ISSN: 0092-8674 the whole document -----</p>	1-36

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 1-36 in part because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-36 in part

Present claims 1-36 relate to an extremely large number of possible compounds, as well as their use. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only the expression of the Smac protein. For the protein-carrier combination, no actual example is given. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds specifically prepared in the examples.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-10 in part, 11 and 13-36

The Smac/carrier entity as claimed, optionally in combination with another cytostatic agent, a medicament for the treatment of cancer containing it, its use in the treatment of autoimmune disease, and the use of an expression plasmid carrying the gene of the Smac protein as claimed for the treatment of cancer

1.1. claims: 1-10 in part, 25

The Smac/carrier entity as claimed, and a medicament for the treatment of cancer containing it.

1.2. claims: 11, 13-24

Use of the Smac/carrier entity as claimed in combination with another anticancer agent, in the treatment of cancer

1.3. claims: 26-28

Use of the Smac/carrier entity as claimed in the treatment of autoimmune diseases

1.4. claims: 29-36

Use of an expression plasmid carrying the gene of the Smac protein as claimed for the treatment of cancer

2. claims: 1-10 in part, and 12

The Smac/carrier entity as claimed in combination with radiation therapy, for use as pharmaceutical

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/04039

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
WO 02016418	A 28-02-2002	AU 8673001 A CA 2420534 A1 EP 1315811 A2 WO 0216418 A2 US 2002132786 A1			04-03-2002 28-02-2002 04-06-2003 28-02-2002 19-09-2002
WO 02016402	A 28-02-2002	US 6608026 B1 AU 9127001 A WO 0216402 A2			19-08-2003 04-03-2002 28-02-2002
WO 02026775	A 04-04-2002	AU 9318901 A AU 9645701 A EP 1346290 A2 WO 0226775 A2 WO 0227534 A2 US 2002177557 A1 US 2003167209 A1			08-04-2002 08-04-2002 24-09-2003 04-04-2002 04-04-2002 28-11-2002 04-09-2003
WO 0149719	A 12-07-2001	US 6110691 A AU 2630701 A CA 2395344 A1 EP 1244787 A2 JP 2003518943 T WO 0149719 A2 US 6534267 B1			29-08-2000 16-07-2001 12-07-2001 02-10-2002 17-06-2003 12-07-2001 18-03-2003
JP 2001046070	A 20-02-2001	NONE			
WO 0058488	A 05-10-2000	AU 4055500 A CA 2368998 A1 EP 1165819 A2 JP 2002539839 T WO 0058488 A2			16-10-2000 05-10-2000 02-01-2002 26-11-2002 05-10-2000
WO 0138547	A 31-05-2001	AU 2508501 A CA 2392490 A1 WO 0138547 A2 EP 1235914 A2 JP 2003514564 T US 2003125242 A1			04-06-2001 31-05-2001 31-05-2001 04-09-2002 22-04-2003 03-07-2003
WO 0029427	A 25-05-2000	AU 766489 B2 AU 1063000 A CA 2350919 A1 CZ 20011671 A3 EP 1135410 A2 WO 0029427 A2 GB 2346616 A HU 0204199 A2 JP 2002530059 T US 2002098236 A1			16-10-2003 05-06-2000 25-05-2000 17-10-2001 26-09-2001 25-05-2000 16-08-2000 28-03-2003 17-09-2002 25-07-2002
WO 9905302	A 04-02-1999	AU 741546 B2 AU 8408098 A EP 0998577 A1 JP 2002511885 T WO 9905302 A1 US 6025140 A			06-12-2001 16-02-1999 10-05-2000 16-04-2002 04-02-1999 15-02-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/EP 03/04039

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 6306613	B1 23-10-2001	US 6083706 A		04-07-2000
		AU 6339198 A		18-09-1998
		CN 1252716 T		10-05-2000
		EP 1011655 A1		28-06-2000
		JP 2001527390 T		25-12-2001
		WO 9837880 A1		03-09-1998
EP 0903408	A 24-03-1999	EP 0903408 A2		24-03-1999
		AT 173016 T		15-11-1998
		AU 667244 B2		14-03-1996
		AU 5083293 A		15-03-1994
		CA 2135642 A1		03-03-1994
		DE 69321962 D1		10-12-1998
		DE 69321962 T2		01-07-1999
		DE 656950 T1		14-03-1996
		DK 656950 T3		19-07-1999
		EP 0656950 A1		14-06-1995
		ES 2123062 T3		01-01-1999
		FI 945248 A		05-01-1995
		HK 1012678 A1		15-09-2000
		JP 2869396 B2		10-03-1999
		JP 10033186 A		10-02-1998
		JP 2702285 B2		21-01-1998
		JP 7503617 T		20-04-1995
		KR 153027 B1		15-10-1998
		NO 944273 A		17-02-1995
		NZ 255831 A		24-04-1997
		WO 9404686 A1		03-03-1994
		US 6316003 B1		13-11-2001
		US 5674980 A		07-10-1997
		US 5670617 A		23-09-1997
		US 5652122 A		29-07-1997
		US 5747641 A		05-05-1998
WO 9404686	A 03-03-1994	AT 173016 T		15-11-1998
		AU 667244 B2		14-03-1996
		AU 5083293 A		15-03-1994
		CA 2135642 A1		03-03-1994
		DE 69321962 D1		10-12-1998
		DE 69321962 T2		01-07-1999
		DE 656950 T1		14-03-1996
		DK 656950 T3		19-07-1999
		EP 0656950 A1		14-06-1995
		EP 0903408 A2		24-03-1999
		ES 2123062 T3		01-01-1999
		FI 945248 A		05-01-1995
		HK 1012678 A1		15-09-2000
		JP 2869396 B2		10-03-1999
		JP 10033186 A		10-02-1998
		JP 2702285 B2		21-01-1998
		JP 7503617 T		20-04-1995
		KR 153027 B1		15-10-1998
		NO 944273 A		17-02-1995
		NZ 255831 A		24-04-1997
		WO 9404686 A1		03-03-1994
		US 6316003 B1		13-11-2001
		US 5674980 A		07-10-1997
		US 5670617 A		23-09-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9404686	A US	5652122 A 5747641 A	29-07-1997 05-05-1998